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(54) Topical preparations containing tars and fatty acids.

(57) A product for topical application against inflammatory and pruritic conditions of the skin which comprises a dermatological tar or tar-based preparation and  $\gamma$ -linolenic acid (GLA) of dihomogamma-linolenic acid (DGLA) as such or in the form of an active derivative thereof.

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"TOPICAL PREPARATIONS CONTAINING TARS AND FATTY ACIDS"

Tar preparations have been used in dermatology for well over a hundred years and still have a major place in the treatment of such conditions as eczema, psoriasis and other inflammatory and pruritic conditions of the skin. The mechanism of action of the tars is  
5 unknown.

The inventor has recently analysed blood samples of seven patients with severe psoriasis before and after a course of treatment with tars. The method of determinations was: Plasma samples (1ml) were extracted with chloroform:methanol (2:1). The extract was  
10 filtered through sodium sulphate, evaporated to dryness, and taken up in 0.5 ml chloroform:methanol. The lipid fractions were separated by thin layer chromatography on silica gel plates. The phospholipid fraction, taken to reflect essential fatty acid changes most sensitively, was methylated using boron trifluoride-methanol.  
15 The resulting methyl esters of the fatty acids were separated and measured using a Hewlett Packard 5880 gas chromatograph with a six foot column packed with 10% silar on chromosorb WAW 106/230. The carrier gas was helium (30 mL/min.). Oven temperature was programmed to rise from 165°C to 190°C at 2°C/min. Detector temperature was  
20 220°C and injector temperature 200°C. Retention times and peak areas were automatically computed by a Hewlett Packard Level 4 integrator. Peaks were identified by comparison with standard fatty acid methyl esters.

The outstanding change in the blood was a rise in the level  
25 of dihom- $\gamma$ -linolenic acid (DGLA) in the plasma from below normal to above normal levels. The normal level of DGLA in human plasma phospholipids, expressed as a percentage of the total fatty acids present, is  $3.06 \pm 0.60$ . In the patients with psoriasis, before treatment with tar, the level was  $2.66 \pm 1.17$ . After treatment, the DGLA level was  $4.03 \pm 1.01$ , a statistically significant increase.

30 The inventor believes that the increase is significant in relation to the therapeutic action of the tars. DGLA gives rise

in the body to prostaglandin  $E_1$ , a substance which has a wide range of desirable effects including the control of several forms of inflammation. This control, and the conversion of DGLA to prostaglandins, are discussed for example in the inventor's published  
5 European Patent Specification No. A 0 004 770 to which reference may be made. Specifically, a rise in plasma DGLA has desirable effects in the treatment of skin disorders such as eczema and psoriasis, and once such a rise has been found to be an effect of tar treatment it suggests that the value of the treatment may be enhanced by giving  
10 DGLA or other materials which give local or systemic rises in DGLA levels.

Thus according to the invention, use of dermatological tars and tar-based preparations (herein referred to generally as tars) has an enhanced therapeutic value if it is combined with use of  
15 dihomog- $\gamma$ -linolenic acid (DGLA) or its precursor  $\gamma$ -linolenic acid (GLA), as such or as active derivatives as detailed later herein. The tars may be used in the ordinary way and the fatty acids either topically with the tars or as oral or other preparations acting through the bloodstream.

20 Primarily the invention lies in a product for topical application which comprises:

1. A dermatological tar or tar-based preparation;
2.  $\gamma$ -linolenic acid or dihomog- $\gamma$ -linolenic acid, whether from natural or synthetic sources, as such or in the form of an active  
25 derivative thereof.

The invention also lies in a method for treatment of inflammatory and pruritic conditions of the skin wherein such a tar or tar preparation is applied in conjunction with systemic or topical use of such acid(s) as derivatives, and to a pack comprising a topical dermatological tar or tar-based preparation and an oral form of GLA  
30 or DGLA or derivative thereof, presented separately but for use together.

Very many tar or tar-based preparations are available. Most are prepared from coal tar, some from pine tar (also known as Stockholm tar) and some from beech, birch or other wood tars. The

chief components of such tars are pitch, benzene, naphthalene, phenols, pyridine and quinoline. The invention may therefore make use for example of Coal Tar BPC, Prepared Coal Tar BP, Tar BP, Pine Tar, Beech Tar or Birch Tar, or any preparation derived from coal or wood tar.

The essential fatty acids may be used as such or in the form of derivatives, particularly natural glyceride esters but also simple esters such as  $C_1 - C_4$  alkyl esters, salts, amides and phospholipids. Such derivatives, having the effect of the acids themselves and pharmacologically acceptable are referred to as active derivatives herein. Indirect identification of useful derivatives is by their having the valuable effect in the body of the acid itself, but conversion can be shown directly by gas chromatographic analysis of concentrations in blood, body fat, or other tissue by standard techniques for example those of Pelick et al p. 23, "Analysis of Lipids and Lipoproteins" Ed. Perkins, American Oil Chemists Society, Champaign, Illinois, U.S.A. The most convenient derivative is the oil of the seed of the Evening Primrose (*Oenothera* spp) the analysis of which is given for example in published European Patent Specification No. 0 004 770 referred to above, containing  $\gamma$ -linolenic acid in glyceride form.

The two components may be combined together in an appropriate topical form such as an ointment, paste, cream, lotion, soap, shampoo or emulsion according to methods in themselves standard in the art or as previously noted they may be used separately.

Examples of products are as follows, all by weight:

1. Coal tar cream: coal tar 2%, 'Cetamacrogol 1000' 5%, isopropyl myristate 22%, wool fat 15%, emulsifying wax 5%, and evening primrose oil, safflower oil or borage oil 2% (or alternatively synthetic GLA or DGLA 0.2%), with water to 100%.
2. Coal tar paste: coal tar solution 5%, evening primrose oil 3%, soft paraffin to 100%.
3. Coal tar ointment: coal tar solution 3%, evening primrose oil 4%, wool alcohols ointment to 100%.

The range of concentration of the tars in such a product is suitably 0.01 to 30%, preferably 1 to 10%, by weight. The range of concentration of evening primrose oil is suitably 0.01 to 30%, preferably 0.2 to 5%, by weight with molar corresponding amounts  
5 of the fatty acids themselves or of other derivatives taking the GLA content of evening primrose oil as 9%, by weight.

The combination of tar and essential fatty acids can be used with other agents conventionally used for skin treatment, such as zinc compounds, salicylates, sulphur, hydrocortisone or other steroids,  
10 iodohydroxyquinoline, lauryl sulphate, resorcinol or benzoyl peroxide. All the products are applied daily in the same way as conventional coal tar preparations.

Further, essential fatty acids as a class have long been known to be important in skin function, and other essential fatty acids may  
15 with benefit be used in the products of the invention in addition to DGLA and GLA. Such acids include arachidonic acid (20:4n-6), adrenic acid (22:4n-6), and 22:5n-6, which will act by sparing DGLA from conversion in the bodily pathway from DGLA to arachidonic and the further acids and possibly by other mechanisms as yet unknown,  
20 and the essential fatty acids of the n-3 series, namely  $\alpha$ -linolenic acid (18:3n-3), 18:4n-3, 20:4n-3, 20:5n-3, 22:5n-3 and 22:6n-3. Amounts may be as for DGLA and GLA.

There are sources of  $\alpha$ -linolenic acid in a variety of vegetable oils such as soy and linseed oils, whereas the longer chain n-3 acids  
25 are found in some abundance in fish oils. Natural sources of arachidonic acid include for example egg yolks, and the higher n-6 acids can be obtained from adrenal glands and kidneys from slaughter houses.

The structures and relations of the acids are as follows:

-5-

	<u>n-6</u>	<u>n-3</u>	<u>Structure</u>
	18:2		$\Delta^{9,12}$ octadecadienoic acid
	↓		
	18:3	18:3	$\Delta^{6,9,12}$ and $\Delta^{9,12,15}$ octadecatrienoic acids
	↓	↓	
		18:4	$\Delta^{6,9,12,15}$ octadecatetraenoic acid
	↓		
5	20:3		$\Delta^{8,11,14}$ eicosatrienoic acid
	↓	↓	
	20:4	20:4	$\Delta^{5,8,11,14}$ and $\Delta^{8,11,14,17}$ eicosatetraenoic acids
	↓	↓	
		20:5	$\Delta^{5,8,11,14,17}$ eicosapentaenoic acid
	↓		
	22:4		$\Delta^{7,10,13,16}$ docosatetraenoic acid
	↓	↓	
	22:5	22:5	$\Delta^{4,7,10,13,16}$ and $\Delta^{7,10,13,16,19}$ docosapentaenoic acid
		↓	
10		22:6	$\Delta^{4,7,10,13,16,19}$ docosahexaenoic acid

The acids are in the natural all-cis configurations. In the n-6 series commonly used names for the 18:2, 18:3, 20:3, 20:4 and 22:4 acids are linoleic acid,  $\gamma$ -linolenic acid (GLA), dihomo- $\gamma$ -linolenic acid (DGLA), arachidonic acid (AA) and adrenic acid. In 15. the n-3 series only  $\alpha$ -linolenic acid (18:3) is commonly referred to by a non-systematic name.

The elongation stages in the natural metabolic pathway are much more rapid than the desaturations. The sequences, believed to be mediated by common enzymes in the two pathways, are:

	<u>n-6</u>	<u>n-3</u>
	18:2	18:3
	$\Delta^6$ desaturase	
	18:3	18:4
5	elongation	
	20:3	20:4
	$\Delta^5$ desaturase	
	20:4	20:5
	elongation	
10	22:4	22:5
	$\Delta^4$ desaturase	
	22:5	22:6

Studies of the interactions between the metabolism of the n-6 acids and that of the n-3 acids have shown that elongation reactions 15 (e.g. GLA to DGLA) are highly efficient and there is very little competition either way. In contrast, the two series of fatty acids compete with one another effectively for the desaturation processes. This means that the n-3 fatty acids will interfere with both  $\Delta$ -6 and  $\Delta$ -5 desaturation in the n-6 series. This competition seems to 20 occur even when the n-3 fatty acid is not actually a substrate for the enzyme concerned. For example, 20:5n-3 competitively inhibits  $\Delta$ -6 desaturation. A consequence of this is that the presence of n-3 fatty acids in a combination will lead to some inhibition of the conversion of DGLA to arachidonic acid by the  $\Delta$ -5-desaturase.

CLAIMS

1. A product for topical application against inflammatory and pruritic conditions of the skin which comprises a dermatological tar or tar-based preparation and  $\gamma$ -linolenic acid (GLA) or dihomogamma-linolenic acid (DGLA) as such or in the form of an active derivative thereof.
- 5 2. A product according to claim 1, comprising further arachidonic acid (20:4n-6), adrenic acid (22:4n-6) or docosapentaenoic acid (22:5n-6) or an essential fatty acid of the n-3 series, namely  $\alpha$ -linolenic acid (18:3n-3) or the 18:4n-3, 20:4n-3, 20:5n-3, 22:5n-3 or 22:6n-3 acid thereof.
- 10 3. A product according to claim 1, comprising further one or more of zinc compounds, salicylates, sulphur, hydrocortisone or other steroids, iodohydroxyquinoline, lauryl sulphate, recorcinol, or benzoyl peroxide, effective against said skin conditions.
4. A product according to claim 1 comprising 0.01 to 30%, preferably  
15 1 to 10%, by weight, of said dermatological preparation.
5. A product according to claim 1, comprising 0.01 to 30%, preferably 0.2 to 5%, by weight, of evening primrose oil or molar corresponding amounts of GLA, DGLA or other derivative thereof (on the basis of a GLA content of evening primrose oil of 9%).
- 20 6. A pack comprising a topical dermatological tar or tar-based preparation and an oral form of GLA or DGLA or derivative thereof, presented separately but for use together.
7. When for use in a method for treatment of inflammatory and  
25 pruritic conditions of the skin, a dermatological tar or tar-based preparation and GLA or DGLA or derivative thereof, and a method wherein such a tar or tar preparation is applied in conjunction with systemic or topical use of such acid or derivative.

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# EUROPEAN SEARCH REPORT

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Application Number

EP 84 30 6415

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
D, Y	EP-A-0 004 770 (VERRONMAY LTD) * Claims 1,8,16-19; page 3, lines 1-5; page 16, lines 33-36; page 17, lines 1-6 *	1-7	A 61 K 35/04 A 61 K 7/48 // (A 61 K 35/04 A 61 K 31:20 )
Y	US-A-4 178 373 (R.W. KLEIN et al.) * Claims 1-3,7; column 2, lines 8-38,51-54 *	1-7	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 30-05-1988	Examiner PEETERS J.C.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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